View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

Body Mass Index and Its Association with Clinical Outcomes for Advanced Non–Small-Cell Lung Cancer Patients Enrolled on Eastern Cooperative Oncology Group Clinical Trials

Suzanne E. Dahlberg, PhD, Joan H. Schiller, MD,† Philip B. Bonomi, MD,‡ Alan B. Sandler, MD,§ Julie R. Brahmer, MD,‖ Suresh S. Ramalingam, MD,¶ and David H. Johnson, MD#*

Introduction: Obesity increases the risk of death from many adverse health outcomes and has also been linked with cancer outcomes. The impact of obesity on outcomes of advanced non–small-cell lung cancer patients is unclear.

Methods: The authors evaluated the association of body mass index (BMI) and outcomes in 2585 eligible patients enrolled in three consecutive first-line trials conducted by the Eastern Cooperative Oncology Group. BMI was categorized as underweight (BMI < 18.5 kg/m^2), normal weight (BMI: 18.5 to < 25 kg/m^2), overweight (BMI: 25 to < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2). In addition to analyzing overall and progression-free survival, reasons for treatment discontinuation were also assessed by BMI group.

Results: Of the patients enrolled, 4.6% were underweight, 44.1% were normal weight, 34.3% of patients were classified as overweight, and 16.9% were obese. Nonproportional hazards existed for obese patients relative to the other three groups of patients, with a change in overall survival hazard occurring at approximately 16 months. In multivariable Cox models, obese patients had superior outcomes earlier on study compared with normal/overweight patients 0.86 (HR=0.86, p=0.04; 95% CI: 0.75–0.99), but later experienced increased hazard (HR=1.54, p< 0.001; 95% CI: 1.22–1.94), indicating a time effect while undergoing treatment.

Conclusion: Data from these three trials suggest differential outcomes associated with BMI, and additional studies of the mechanisms underlying this observation, as well as dietary and lifestyle interventions, are warranted to help optimize therapy.

Key Words: Body mass index, Weight, Obesity, Non–small-cell lung cancer, Advanced disease, First-line therapy, Phase III, Chemotherapy, Bevacizumab.

(*J Thorac Oncol.* 2013;8: 1121-1127)

Elevated body mass index (BMI), defined as weight in kilograms divided by the square of the height in meters, increases the risk of death from many adverse health outcomes and continues to remain a significant public health problem in developed nations such as the United States, Canada, and Europe.[1] BMI-defined overweight and obesity, which affect nearly two thirds of the U.S. population and continue to increase in prevalence, are associated with increased risk of cardiovascular disease, diabetes, arthritis, and asthma, as well as colon, breast, endometrial, and renal cancers.[2–6] With respect to lung cancer, however, many investigations have demonstrated an inverse association between BMI and risk of fatal lung cancers.[7–18]

Despite the wealth of literature detailing the association between BMI and lung cancer incidence, studies evaluating the relationship of BMI on outcomes for patients with lung cancer are somewhat limited.[19] To our knowledge these studies have not focused on lung cancer patients enrolled in clinical trials, which select for patients with fewer comorbidities by way of their eligibility criteria; trials typically require good performance status (PS), adequate organ function, and limited exposure to major surgery or treatments within a reasonable timeframe of study entry. Increased BMI has also been associated with improved outcomes for patients with renal cell cancer and diffuse large B-cell lymphoma, but with poorer prognosis in patients with colon, prostate, and breast cancers.[3,20–22] It is therefore of interest to study whether or not the association between BMI and clinical outcomes can be validated in this setting.

The current study presents results from an analysis of the clinical course of advanced non–small-cell lung cancer (NSCLC) patients enrolled in the most recent three front-line phase III trials, E5592, E1594, and E4599, conducted

*Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, Massachusetts; †Division of Hematology-Oncology, University of Texas Southwestern Medical Center, Dallas, Texas; ‡Department of Medical Oncology, Rush University Medical Center, Chicago, Illinois; §Division of Hematology and Medical Oncology, Oregon Health and Science University, Portland, Oregon; ‖Department of Medical Oncology, Johns Hopkins University, Baltimore, Maryland; ¶Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, Georgia; and Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Suzanne E. Dahlberg, PhD, Department of Biostatistics and Computational Biology, CLSB 11007, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215. E-mail: dahlberg@jimmy.harvard.edu

Copyright © 2013 by the International Association for the Study of Lung Cancer

ISSN: 1556-0864/13/0809-1121

TABLE 1. Eastern Cooperative Oncology Phase III First-Line Trials in Advanced Non–Small-Cell Lung Cancer, 1993–2004

Study	Regimens	Accrual Period	No. of Patients with BMI Data
E5592: Bonomi et al., 2000	Cisplatin (75 mg/m^2) + etoposide (100 mg/m^2)	1993–94	574
	Cisplatin (75 mg/ m^2) + paclitaxel (250 mg/m^2)		
	Cisplatin (75 mg/ m^2) + paclitaxel (135 mg/m^2)		
E1594: Schiller et al., 2002	Cisplatin (75 mg/ m^2) + paclitaxel (135 mg/m^2)	1996–99	1161
	Cisplatin (100 mg/ m^2) + gemcitabine (1000 mg/ m^2)		
	Cisplatin (75 mg/ m^2) + docetaxel (75 mg/ m^2)		
	Carboplatin, AUC 6.0 mg/ml/min + paclitaxel (225 mg/ m^2)		
E4599: Sandler et al. 2006	Carboplatin, AUC 6.0 mg/ml/min + paclitaxel (200 mg/m^2) + bevacizumab (15 mg/kg)	2001–04	850
	Carboplatin, AUC 6.0 mg/ml/min + paclitaxel (200 mg/m^2)		

AUC, area under the curve; BMI, body mass index.

by the Eastern Cooperative Oncology Group (ECOG) in this patient population. Statistical endpoints included overall survival (OS), progression-free survival (PFS), best objective response, toxicity, and time to treatment discontinuation. To our knowledge, this study is the first to analyze these data using prospectively collected treatment and eligibility criteria and to include detailed information on underweight patients.

PATIENTS AND METHODS

Study Population

During the period from 1993 to 2004, the ECOG enrolled 2684 patients to three phase III trials of first-line systemic chemotherapy for advanced NSCLC. In brief, eligible patients had stage IIIB, IV, or recurrent disease, ECOG PS 0 to 1, no prior systemic chemotherapy, and adequate bone marrow, hepatic, and renal function. Per protocol, all patients were dosed based on actual weight. Additional details regarding eligibility, treatment, and results have been reported elsewhere and are summarized in Table 1; E1594 enrolled 65 eligible patients with PS 2 before a protocol amendment restricted eligibilty to ECOG PS of 0 or 1 only.[23–25] The primary endpoint of these trials was OS, and the primary analyses were conducted among all eligible patients. Each participant gave informed consent. These studies were conducted in accordance with the Declaration of Helsinki, current Food and Drug Administration Good Clinical Practices, and local institutional review board requirements.

Statistical Methods

Baseline patient demographics and disease characteristics were compared using Fisher's exact test. OS, the primary endpoint considered, was defined as time interval in months from randomization to death from any cause. PFS was defined as the time interval in months from randomization to documented progression or death. Patients not experiencing an event were censored at the last date of follow-up for OS and the last date of disease assessment for PFS. Time-to-event distributions were estimated using the Kaplan–Meier method, and comparisons of these distributions were made using the log-rank test.[26] Multivariable piecewise Cox proportional hazards models were used to estimate hazard ratios (HRs) for OS and PFS.[27] Response and toxicity on protocols E5592 and E1594 were assessed using ECOG criteria; for E4599, the Response Evaluation Criteria in Solid Tumors version 1.0 and Common Terminology Criteria for Adverse Events version 2.0 were used. The cumulative incidence function of time to treatment discontinuation because of toxicity, adjustment for death, progression, and withdrawal/other as competing events was constructed using the method of Kalbfleish and Prentice.[28] All p values are two-sided, confidence intervals (CIs) are at the 95% level, and no adjustments have been made for multiple comparisons.

BMI at the time of randomization was defined as weight in kilograms divided by the square of the height in meters. Patients were stratified into BMI groups defined by the World Health Organization: underweight (BMI < 18.5 kg/m^2), normal weight (BMI: 18.5 to < 25 kg/m^2), overweight (BMI: 25 to < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2).[20,29]

RESULTS

At a median follow-up of 64.9 months, 2585 of the 2684 patients (96.3%) randomized on these trials were declared eligible and constituted the primary analysis population; all had BMI measurements at the time of study registration. Table 2 displays the baseline patient demographics and disease characteristics of the study cohort by BMI group. Consistent with the general population, 4.6% of patients were underweight, 44.1% were normal weight, 34.3% of patients were classified as overweight, and 16.9% were obese. Most of the baseline demographics and disease characteristics were significantly imbalanced by BMI group, with the exception of stage, histology, prior surgery, pleural involvement, liver metastases, and baseline serum albumin. Underweight patients were more likely to be younger, African American, female, have worse ECOG PS, have more weight loss and radiotherapy before study enrollment, and be enrolled on the more recent trials.

Figure 1 displays the results of the OS analysis by BMI group. Of 2585 patients, 2353 (91%) had died at the time of this analysis. The median OS estimated among underweight patients was 7.0 months (95% CI: 5.5–9.6), among normal-weight patients was 8.6 months (95% CI: 8.0–9.4), among overweight patients was 9.3 months (95% CI: 8.6–10.1), and among obese patients was 11.0 months (95% CI: 10.2–11.9).

Copyright © 2013 by the International Association for the Study of Lung Cancer

TABLE 2. Distribution of Baseline Patient Demographics and Disease Characteristics by BMI

	Underweight		Normal Weight		Overweight		Obese			
	BMI < 18.5 kg/m²		18.5 ≤ BMI < 25 kg/m²		25 ≤ BMI < 30 kg/m²		BMI ≥ 30 kg/m²		Total	
	(*n* = 123)		(*n* = 1139)		(*n* = 887)		(*n* = 436)		(N = 2585)	
Protocol ($p = 0.004$)										
E5592	34	27.6%	276	24.2%	191	21.5%	73	16.7%	574	22.2%
E1594	59	48.0%	514	45.1%	391	44.1%	197	45.2%	1161	44.9%
E4599	30	24.4%	349	30.6%	305	34.4%	166	38.1%	850	32.9%
Age ($p = 0.003$)										
Median (range)	59	35–83	61	29–85	62	25–86	63	31–88	62	25–88
Race ($p = 0.01$)										
White	94	76.4%	971	85.5%	779	87.8%	376	86.4%	2220	86.0%
Black	21	17.1%	93	8.2%	62	7.0%	33	7.6%	209	8.1%
Other	8	6.5%	72	6.3%	46	5.2%	26	6.0%	152	5.9%
Sex ($p = 0.001$)										
Male	58	47.2%	678	59.5%	572	64.5%	249	57.1%	1557	60.2%
Female	65	52.8%	461	40.5%	315	35.5%	187	42.9%	1028	39.8%
ECOG PS ($p < 0.001$)										
0	27	22.0%	347	30.6%	336	37.9%	163	37.5%	873	33.9%
1	89	72.4%	761	67.0%	532	60.0%	259	59.5%	1641	63.6%
2	7	5.7%	27	2.4%	18	2.0%	13	3.0%	65	2.5%
Prior weight loss ($p < 0.001$)										
<5%	44	35.8%	697	61.2%	687	77.5%	366	83.9%	1794	69.4%
≥5%	79	64.2%	441	38.8%	200	22.5%	70	16.1%	790	30.6%
Unknown			1						1	
Stage ($p = 0.13$)										
IIIB	11	8.9%	152	13.3%	114	12.9%	68	15.6%	345	13.4%
IV	97	78.9%	839	73.7%	647	73.0%	294	67.4%	1877	72.6%
Recurrent	15	12.2%	148	13.0%	125	14.1%	74	17.0%	362	14.0%
Histology ($p = 0.43$)										
Squamous	16	13.0%	161	14.2%	120	13.5%	58	13.3%	355	13.7%
Adenocarcinoma	66	53.7%	693	60.9%	548	61.8%	277	63.5%	1584	61.3%
Other	41	33.3%	283	24.9%	219	24.7%	101	23.2%	644	24.9%
Prior RT ($p = 0.02$)										
Yes	25	20.3%	234	20.5%	143	16.1%	67	15.4%	469	18.2%
No	98	79.7%	905	79.5%	743	83.9%	368	84.6%	2114	81.8%
Prior surgery ($p = 0.84$)										
Yes	42	34.4%	415	36.6%	319	36.1%	166	38.2%	942	36.6%
No	80	65.6%	719	63.4%	564	63.9%	268	61.8%	1631	63.4%
Pleura involvement ($p = 0.94$)										
Yes	37	30.1%	352	30.9%	263	29.7%	131	30.0%	783	30.3%
No	86	69.9%	787	69.1%	624	70.3%	305	70.0%	1802	69.7%
Liver mets ($p = 0.19$)										
Yes	30	24.4%	237	20.8%	164	18.5%	80	18.3%	511	19.8%
No	93	75.6%	902	79.2%	723	81.5%	356	81.7%	2074	80.2%
Serum Albumin ($p = 0.89$)										
Median (range)	3.6	2.1–5.1	3.7	0–8.4	3.8	1.7–8.2	3.9	2.1–5.0	3.8	0–8.4

BMI, body mass index; ECOG, Eastern Oncology Group; PS, performance status; RT, radiotherapy.

A logrank test for differences in these four OS distributions was statistically significant ($p = 0.005$), though it is important to note that there was no statistically significant difference in OS between normal-weight and overweight patients ($p = 0.11$). Visual inspection of the OS Kaplan–Meier curves as well as a formal test for proportional hazards using a test based on Schoenfeld residuals leads to the conclusion that nonproportional hazards exist for obese patients relative to

Copyright © 2013 by the International Association for the Study of Lung Cancer

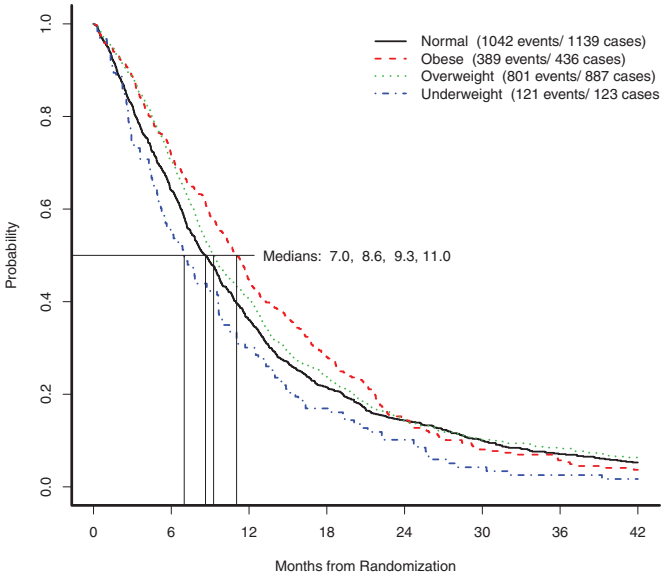


FIGURE 1. Overall survival by body mass index.

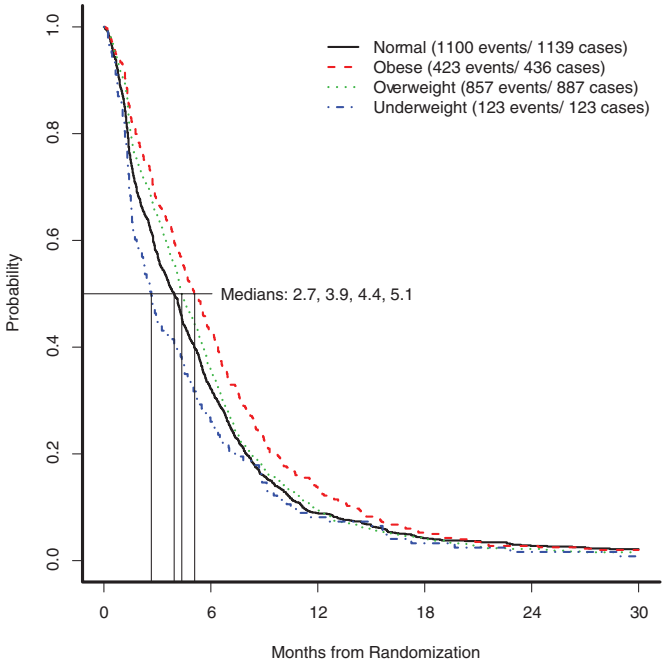


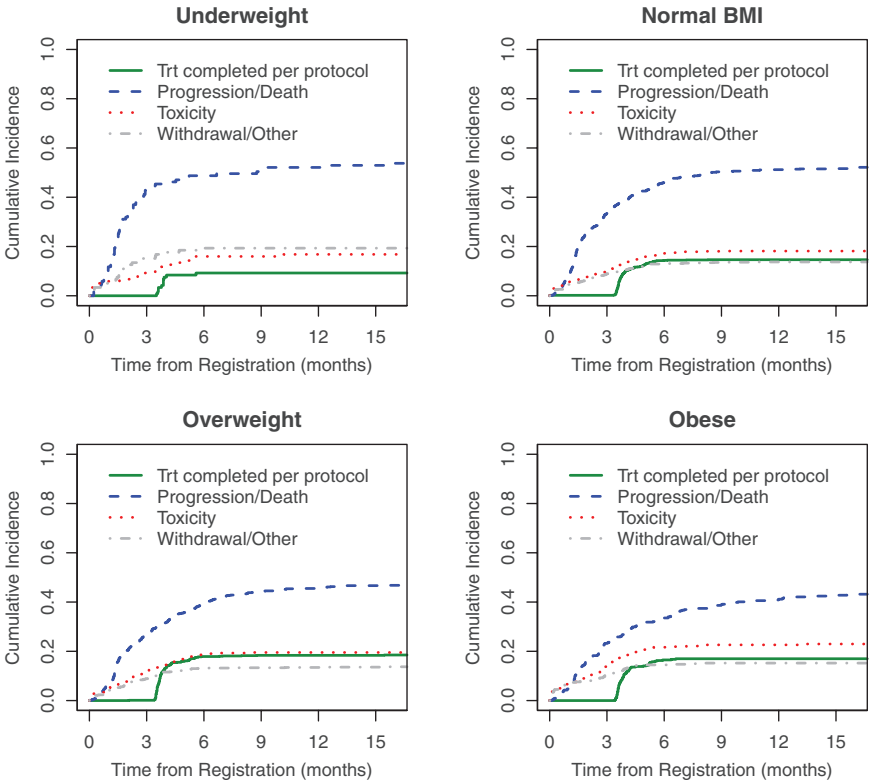
FIGURE 2. Progression-free survival by body mass index.

the other three groups of patients; specifically, the hazard for obese patients seems to begin increasing at approximately 16 months postrandomization.[30–32] At this timepoint, a total of 656 patients remained in follow-up: 23 underweight patients, 266 normal-weight patients, 225 overweight patients, and 142 obese patients. To account for this in the analysis of OS, piecewise Cox models estimating the HR of obese patients relative to the combined group of normal-weight and overweight patients adjusting for time as a time-varying covariate were fitted, stratified by protocol to account for any potential trends in BMI over time, as well as protocol effects; the HR comparing underweight patients with normal-weight/overweight patients was also estimated. In a model unadjusted for other baseline prognostic factors, the estimated OS HR comparing underweight patients with normal-weight/overweight patients was 1.26 ($p = 0.01$; 95% CI: 1.05–1.51); the estimated OS HR comparing obese patients whose days on study was less than 16 months from randomization with normal-weight/overweight patients was 0.81 ($p = 0.001$; 95% CI: 0.71–0.92). When time on study exceeded 16 months, obese patients experienced a significant increase in their OS hazard rate relative to normal-weight/overweight patients, with an estimated OS HR of 1.31 ($p = 0.02$; 95% CI: 0.62–0.95). After adjusting for sex (female versus male, HR = 0.83; $p < 0.001$), ECOG PS (1/2 versus 0; HR = 1.40; $p < 0.001$), stage (IV/recurrent versus IIIB; HR = 1.37; $p < 0.001$), presence of liver metastases (HR = 1.39; $p < 0.001$), weight loss (>5% in the previous 6 months; HR = 1.26; $p < 0.001$), and elevated baseline albumin (>3.8; HR = 0.67; $p < 0.001$), all of which were chosen using backward stepwise selection and statistically significant, the estimated OS HR comparing underweight patients with normal-weight/overweight patients was 1.12 ($p = 0.29$; 95% CI: 0.91–1.37), and comparing obese patients whose days postregistration were less than 16 months with normal-weight/overweight patients was 0.86 ($p = 0.04$; 95% CI: 0.75–0.99). When time on study exceeded 16 months, obese patients experienced a significant increase in their OS hazard rate relative to normal-weight/overweight patients, with an estimated OS HR of 1.54 ($p < 0.001$; 95% CI: 1.22–1.94).

At the time of last follow-up, 2503 patients (97%) had experienced a PFS event. The median PFS estimated among underweight patients was 2.7 months (95% CI: 2.0–4.0), among normal-weight patients was 3.9 months (95% CI: 3.6–4.3), among overweight patients was 4.4 months (95% CI: 4.2–4.8), and among obese patients was 5.1 months (95% CI: 4.5–5.7). A logrank test for differences in these four PFS distributions was statistically significant ($p = 0.001$); the results are displayed in Figure 2. In an unadjusted Cox model stratified on protocol, the estimated PFS HR comparing underweight patients with normal-weight/underweight patients was 1.19 ($p = 0.06$; 95% CI: 0.99–1.43); comparing obese patients with normal-weight/underweight patients, the estimated PFS HR was 0.85 ($p = 0.002$; 95% CI: 0.76–0.94). After adjusting for the same prognostic variables included in the multivariable OS Cox models (sex [HR = 0.91; $p = 0.03$], ECOG PS [HR = 1.24; $p < 0.001$], stage [HR = 1.42; $p < 0.001$], presence of liver metastases [HR = 1.19; $p = 0.002$], weight loss [HR = 1.21; $p < 0.001$], and elevated baseline albumin [HR = 0.76; $p < 0.001$]), the adjusted HRs were 1.04 ($p = 0.73$; 95% CI: 0.85–1.27) for underweight patients and 0.92 ($p = 0.13$; 95% CI: 0.82–1.03) for obese patients, when comparing each of these two groups with normal-weight/overweight patients.

We next assessed the best objective response rates for patients treated on these three protocols across the four BMI groups. Among underweight patients, the response rate was 13.8% compared with 20.5% among normal-weight patients, 22.5% among overweight patients, and 21.3% among obese patients ($p = 0.15$). There were also no significant differences

Copyright © 2013 by the International Association for the Study of Lung Cancer



	Underweight		Normal BMI		Overweight		Obese	
	%	SD	%	SD	%	SD	%	SD
Per protocol	9.2	2.7	14.6	1.1	18.4	1.3	17.0	1.8
Progression/death	52.3	4.7	51.6	1.5	46.7	1.7	42.3	2.5
Toxicity	16.8	3.5	18.1	1.2	19.5	1.4	23.0	2.1
Withdrawal/Other	19.3	3.7	13.7	1.0	13.6	1.2	15.2	1.8

FIGURE 3. Cumulative incidence of treatment discontinuation by BMI, as well as 15-month point estimates and their corresponding SDs. BMI, body mass index; SD, standard deviation.

observed in the rates of grade 3 or higher hematological toxicities across BMI groups: 39.3%, 45.1%, 44.6%, and 40.0% within the underweight, normal-weight, overweight, and obese groups, respectively ($p = 0.20$). Similarly, there were no significant imbalances observed in the rates of grade 3 or higher nonhematological toxicities: 61.5%, 62.4%, 62.2%, and 67.4% within the underweight, normal-weight, overweight, and obese groups, respectively ($p = 0.24$).

We next explored the time to treatment discontinuation to assess whether or not the differences in outcome by BMI group could be explained in part by protocol compliance. The 15-month point estimates for the cumulative incidence rates and their corresponding standard deviations are reported beneath the cumulative incidence curves in Figure 3. The percentage of patients discontinuing treatment because of progression or death was highest among underweight patients (52.3%) and decreased with BMI to 42.3% among obese patients; the rate of discontinuation because of patient withdrawal and other reasons followed a similar inverse trend with BMI. The rate of treatment discontinuation per protocol increased with BMI; however, it was estimated to be 9.2% among underweight patients and increased to 17.0% among obese patients. Obese patients were also more likely to discontinue treatment because of adverse events (23.0%) than those with lower BMI, with a rate of 16.8% among underweight patients. In a regression model of subdistribution functions in competing risks, these results were significantly different across BMIs ($p = 0.004$).

DISCUSSION

In this retrospective analysis of 2585 patients with advanced NSCLC enrolled in three ECOG clinical trials, we assessed the relationship between BMI and clinical outcomes. In multivariable models, obese patients had significantly different OS when compared with normal-weight and overweight patients; however, their risk of death from any cause increased dramatically once they had been on study longer than 16 months. This indicates that the protective effect of obesity in lung cancer patients is for a limited time, after which the ultimate impact of obesity on survival from all causes supersedes. Though not statistically significant, there was a trend toward worse outcomes for underweight patients when compared with normal-weight/overweight patients.

These results are consistent with the limited number of previous studies evaluating the role of BMI on outcomes for NSCLC patients and on risk of lung cancer, but this report

Copyright © 2013 by the International Association for the Study of Lung Cancer

addresses several of the limitations of previous analyses by including prospectively defined and collected study data, uniform staging, and preselection of patients with good PS, cardiac/organ function, and otherwise lower symptom burden and complicating comorbid illness. In our study, we have also evaluated the reasons why patients stopped protocol treatment by BMI group, and found that the outcomes associated with higher BMI occur in accordance with lower rates of withdrawal from study and despite a higher rate of treatment discontinuation because of toxicity. One reason for this observation may be the differential pharmacokinetics resulting in higher chemotherapy dosing among BMI groups; however, it is also possible that patients with lower BMI at the time of enrollment have more aggressive disease and worse nutritional status, subjecting them to more cachexia and subsequently more rapid cancer cell growth.

The time dependence of obesity on outcome relative to patients with normal-weight or underweight status at the time of diagnosis is an interesting observation. One biological reason contributing to this observation may lie in the synergy that exists between peroxisome proliferator–activated receptor ligands, which include natural compounds such as fatty acids and antidiabetic drugs, and platinum-based agents, which has been shown to increase the efficacy of platinum by as much as fourfold in preclinical studies.[33] Because second-line therapies for advanced NSCLC do not include platinum agents as standard of care, the rapid decline in obese patients late in their course of follow-up on these trials could be attributed to the absence of cisplatin or carboplatin after progression, thereby decreasing the synergy with peroxisome proliferator–activated receptor ligands. Other research has implied that metabolic drugs such as phenformin and metformin induce apoptosis in liver kinase B1 (LKB1)-deficient NSCLC; given that LKB1 is inactivated approximately 20% of NSCLC, and that obese patients have a reasonable likelihood of receiving antidiabetic drugs, the superior outcomes early on in their course of cancer treatment could be driven largely by interactions with these concomitant medications. We unfortunately do not have details on the prevalence of diabetes, concomitant medications, or on differences in treatment at progression, to address these hypotheses.[33–35] It is important to note that our results contradict evidence that insulin-like growth factor 1 (IGF-1), a hormone associated with obesity, promotes tumor growth.[36]

A limitation of our study is that smoking status, a confounding variable known to be associated with lower BMI, was not collected on any of these clinical trials, but it was recently reported that residual confounding because of smoking status did not contribute to the inverse relationship between BMI and risk of lung cancer in a prospective cohort study.[7] Despite eligibility criteria that select for good-prognosis patients, we do not have details on patient comorbidities, which may supersede the effects of treatment, expose the patients to excess risk later in their disease trajectory, and thereby explain the change in hazard for obese patients.

Our results are consistent with observational studies demonstrating an inverse association between BMI and risk of fatal lung cancers, as well as with outcomes for patients with lymphoma and renal cancer.[7–18,20,21] This obesity paradox has also been described in other areas of medicine including acute lung injury, septic shock, heart failure, and Human Immunodeficiency Virus.[37–40] Because obesity is associated with more comorbidities and other adverse health conditions, the inverse association between BMI and survival seems intuitively discordant; one explanation for this may be in how our studies and others have defined being overweight and obese. BMI is a numerical measure of both fat mass and muscle mass, and is therefore not the most accurate measure of body fat. Other methods of evaluating true body fat, such as waist circumference and weight to height ratio, as well as cardiorespiratory and muscular fitness have suggested an important role in the obesity paradox, but these methods were unfortunately not available for analysis in our study.[41]

The ideal situation would be conducting an analysis of serial weight measurements over the entire postrandomization timeframe, because the rapid decline of the obese patients could be because they lose so much weight that they become normal-weight or underweight at that point in time. Unfortunately, these data are not available for our studies. This type of information is traditionally collected on treatment forms, which are submitted at each treatment cycle while a patient remains on protocol treatment.

A limitation of our analysis is that some of the treatment regimens were administered for as short a timeframe as six cycles of 3 weeks each or until documented disease progression, at which time protocol therapy would be discontinued and treatment forms would no longer be collected—this is actually fairly standard for clinical trials reporting. With a median PFS of approximately 4 months in this population, this leaves us with scarce data to conduct a robust analysis of BMI over time until death. It is important to note, however, that analyses of weight change over time do not allow for clinical decision making about best course of therapy for patients at baseline, when they present with untreated metastatic disease. That being said, weight gain has been shown to be an important factor in outcomes for patients with locally advanced NSCLC, and serial weight measurements may inform other studies, such as those on renal function.[42–44]

In summary, higher BMI among patients with advanced NSCLC enrolled in three National Cancer Institute–funded Cooperative Group clinical trials is associated with significantly differential survival; however, further studies of the mechanisms underlying this observation, as well as dietary and lifestyle interventions, are warranted to help optimize therapy.

ACKNOWLEDGMENTS

This study was coordinated by the Eastern Cooperative Oncology Group (Robert L. Comis, M.D., Chair) and supported in part by Public Health Service Grants CA23318, CA66636, CA21115, CA49957, CA21076, CA49883, CA16116 and from the National Cancer Institute, National Institutes of Health, and the Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

 Copyright © 2013 by the International Association for the Study of Lung Cancer

REFERENCES

1. Flegal KM, Carroll MD, Kit BK, et al. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. *JAMA* 2012;307:491—497.
2. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA* 2003;289:76—79.
3. Halabi S, Ou SS, Vogelzang NJ, Small EJ. Inverse correlation between body mass index and clinical outcomes in men with advanced castration-recurrent prostate cancer. *Cancer* 2007;110:1478–1484.
4. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004;4:579–591.
5. Renehan AG, Soerjomataram I, Leitzmann MF. Interpreting the epidemiological evidence linking obesity and cancer: a framework for population-attributable risk estimations in Europe. *Eur J Cancer* 2010;46: 2581–2592.
6. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;371:569–578.
7. Smith L, Brinton LA, Spitz MR, et al. Body mass index and risk of lung cancer among never, former, and current smokers. *J Natl Cancer Inst* 2012;104:778–789.
8. Andreotti G, Hou L, Beane Freeman LE, et al. Body mass index, agricultural pesticide use, and cancer incidence in the Agricultural Health Study cohort. *Cancer Causes Control* 2010;21:1759–1775.
9. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003;348:1625–1638.
10. Henley SJ, Flanders WD, Manatunga A, Thun MJ. Leanness and lung cancer risk: fact or artifact? *Epidemiol* 2002;13:268–276.
11. Kabat GC, Kim M, Hunt JR, Chlebowski RT, Rohan TE. Body mass index and waist circumference in relation to lung cancer risk in the Women's Health Initiative. *Am J Epidemiol* 2008;168:158–169.
12. Kabat GC, Miller AB, Rohan TE. Body mass index and lung cancer risk in women. *Epidemiol* 2007;18:607–612.
13. Knekt P, Heliövaara M, Rissanen A, et al. Leanness and lung-cancer risk. *Int J Cancer* 1991;49:208–213.
14. Leung CC, Lam TH, Yew WW, Chan WM, Law WS, Tam CM. Lower lung cancer mortality in obesity. *Int J Epidemiol* 2011;40:174–182.
15. Olson JE, Yang P, Schmitz K, Vierkant RA, Cerhan JR, Sellers TA. Differential association of body mass index and fat distribution with three major histologic types of lung cancer: evidence from a cohort of older women. *Am J Epidemiol* 2002;156:606–615.
16. Samanic C, Chow WH, Gridley G, Jarvholm B, Fraumeni JF Jr. Relation of body mass index to cancer risk in 362,552 Swedish men. *Cancer Causes Control* 2006;17:901–909.
17. Tsai SP, Donnelly RP, Wendt JK. Obesity and mortality in a prospective study of a middle-aged industrial population. *J Occup Environ Med* 2006;48:22–27.
18. Yang L, Yang G, Zhou M, et al. Body mass index and mortality from lung cancer in smokers and nonsmokers: a nationally representative prospective study of 220,000 men in China. *Int J Cancer* 2009;125:2136–2143.
19. Yang R, Cheung MC, Pedroso FE, Byrne MM, Koniaris LG, Zimmers TA. Obesity and weight loss at presentation of lung cancer are associated with opposite effects on survival. *J Surg Res* 2011;170:e75–e83.
20. Carson KR, Bartlett NL, McDonald JR, et al. Increased body mass index is associated with improved survival in United States veterans with diffuse large B-cell lymphoma. *J Clin Oncol* 2012;30:3217–3222.
21. Waalkes S, Merseburger AS, Kramer MW, et al. Obesity is associated with improved survival in patients with organ-confined clear-cell kidney cancer. *Cancer Causes Control* 2010;21:1905–1910.
22. Sparano JA, Wang M, Zhao F, et al. Obesity at diagnosis is associated with inferior outcomes in hormone receptor-positive operable breast cancer. *Cancer* 2012;118:5937–5946.
23. Bonomi P, Kim K, Fairclough D, et al. Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 2000;18:623–631.
24. Schiller JH, Harrington D, Belani CP, et al.; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–98.
25. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542–2550.
26. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457–481, 1958.
27. Cox DR, Oates D. Regression models and life tables. *J Royal Stat Soc* B34:187–220, 1972.
28. Klabfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. New York: Wiley; 1980.
29. World Health Organization. Global database on body mass index. Available at: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html Accessed November 1, 2012.
30. Grambsch P and Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. *Biom* 1994;81:515–26.
31. Schoenfeld D. Chi-squared goodness of fit tests for the proportional hazards regression model. *Biom* 1980;67:145–53.
32. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biom* 1982;69:239–241.
33. Girnun GD, Naseri E, Vafai SB, et al. Synergy between PPARgamma ligands and platinum-based drugs in cancer. *Cancer Cell* 2007;11: 395–406.
34. Wu N, Gu C, Gu H, Hu H, Han Y, Li Q. Metformin induces apoptosis of lung cancer cells through activating JNK/p38 MAPK pathway and GADD153. *Neoplasma* 2011;58:482–490.
35. Shackelford DB, Abt E, Gerken L, et al. LKB1 inactivation dictates therapeutic response of non-small cell lung cancer to the metabolism drug phenformin. *Cancer Cell* 2013;23:143–158.
36. Moschos SJ, Mantzoros CS. The role of the IGF system in cancer: from basic to clinical studies and clinical applications. *Oncol* 2002;63:317–332.
37. O'Brien JM Jr, Phillips GS, Ali NA, Lucarelli M, Marsh CB, Lemeshow S. Body mass index is independently associated with hospital mortality in mechanically ventilated adults with acute lung injury. *Crit Care Med* 2006;34:738–744.
38. Wurzinger B, Dünser MW, Wohlmuth C, et al. The association between body-mass index and patient outcome in septic shock: a retrospective cohort study. *Wien Klin Wochenschr* 2010;122:31–36.
39. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol* 2009;53: 1925–1932.
40. Hanrahan CF, Golub JE, Mohapi L, et al. Body mass index and risk of tuberculosis and death. *AIDS* 2010;24:1501–1508.
41. Lavie CJ, De Schutter A, Patel DA, Milani RV. Body composition and fitness in the obesity paradox-Body mass index alone does not tell the whole story. *Prev Med* March 29, 2013. doi: 10.1016/j.ypmed.2013.03.010. [Epub ahead of print].
42. Sher DJ, Gielda BT, Liptay MJ, et al. Prognostic significance of weight gain during definitive chemoradiotherapy for locally advanced non-small-cell lung cancer. *Clin Lung Cancer* December 20, 2012. doi: 10.1016/j.cllc.2012.10.009. [Epub ahead of print].
43. Gielda BT, Mehta P, Khan A, et al. Weight gain in advanced non-small-cell lung cancer patients during treatment with split-course concurrent chemoradiotherapy is associated with superior survival. *Int J Radiat Oncol Biol Phys* 2011;81:985–991.
44. Kutluk Cenik B, Sun H, Gerber DE. Impact of renal function on treatment options and outcomes in advanced non-small cell lung cancer. *Lung Cancer* 2013;80:326–332.

Copyright © 2013 by the International Association for the Study of Lung Cancer